REMARKS

Claims 1 through 3, 6 through 12 and 14 through 18 and new Claims 19 and 20 are pending in the application.

Claim 1 has been amended to reflect that the first active ingredient-containing polymer layer is advantageously disposed directly on the backing layer. Support for this amendment can be found in the Application-as-filed, for example on Page 12, lines 15 through 25.

Claim 18 has been amended to reflect advantageous transdermal therapeutic systems that have no additional pressure sensitive adhesive top plaster for fixing to the skin. Support for this amendment can be found in the Application-as-filed, for example on Page 5, lines 10 through 15.

Claim18 has also been amended to emphasize advantageous transdermal therapeutic systems in which the first and second active ingredient-containing polymer layers include pressure-sensitive adhesive polymer consisting of carboxyl group-free polyacrylates that do not comprise water or an aqueous dispersion. Support for this amendment can be found in the Application-as-filed, for example on Page 8, lines 18 through 23.

Claims 19 and 20 have been added to complete the record for examination and highlight advantageous embodiments of the invention.

Claim 19 is directed to advantageous transdermal therapeutic systems in which the first and second active ingredient-containing polymer layers include pressure-sensitive adhesive polymer consisting of carboxyl group-free polyacrylates that do not comprise water or an aqueous dispersion and that further provide the recited pramipexol flux rate in the absence of a penetration-promoter and without an additional pressure sensitive adhesive top plaster for fixing to the skin. Support for Claim 19 can be found in the Application-as-filed, for example on Page 8, lines 7 through 23 and Page 5, lines 10 through 15

Claim 20 is directed to advantageous aspects of such embodiments in which the first and second active ingredient-containing polymer layers consist of pramipexol and carboxyl group-free polyacrylate pressure-sensitive adhesive. Support for Claim 20 can be found in the Application-as-filed, for example on Page 12, lines 15 through 29.

Reexamination and reconsideration of this application, withdrawal of all rejections, and formal notification of the allowability of the pending claims are earnestly solicited in light of the remarks which follow.

112 Rejection

Claim 18 stands rejected over the recitation "pressure sensitive top plaster." Without addressing the merits of the rejection and solely to advance prosecution of the case, Claim 18 has been amended to recite "pressure sensitive adhesive top plaster for fixing to the skin," as kindly suggested by the Examiner. Accordingly, Applicants respectfully request withdrawal of the foregoing rejection.

The Claimed Invention is Patentable
in Light of the Art of Record

Claims 1 through 3, 6 through 12, and 14 through 18 stand rejected over WIPO Published Application WO 03/015779, whose United States Equivalent is United States Publication 2004/0247656, which has subsequently matured into United States Patent No. 7,344,733 (US 733) to Beier et al. in view of United States Patent No. 5,939,094 (US 094) to Durif et al and United States Patent No. 4,769,028 (US 028) to Hoffmann et al in view of United States Patent No. 5,112,842 (US 842) to Zierenberg et al. and WIPO publication WO 96/39136 (WO 136) to Patel et al. Claim 16 stands rejected over US 733, US 094, US 842 and WO 136 and further in light of United States Patent No. 5,238,944 (US 944) to Wick et al.

It may be useful to consider the invention as recited in the claims before addressing the merits of the rejection.

Applicants respectfully reiterate that transdermal therapeutic systems ("TTSs") provide a promising option for the continuous delivery of active ingredients over a prolonged period of time. However, the deliver of an active ingredient continuously and in a controlled manner to and through a patient's skin for a prolonged period of time is incredibly challenging.

A significant quantity of the active ingredient must be incorporated into the TTS to provide a sufficient level of diffusion over an extended period of time. The incorporation of such elevated amounts of active ingredients within polymer matrices can be extremely detrimental to the resulting polymer properties, as evidenced in newly cited US 028 at Col. 4, lines 27 through 31. Active ingredients are known to cause polymers to lose their adhesive properties, for instance, resulting in a loss of interlaminar cohesion and structural stability. To impart structural stability and cohesion, an intermediary adhesive layer containing no active ingredient may be incorporated between the active-ingredient matrix and the backing layer, as evidenced in US 028. To address inadequate adhesion to the skin, conventional TTSs to-date have incorporated covering plasters, as evidenced in cited US 842.

In addition to matrix polymer issues, TTSs must also provide active ingredient in a form that adequately penetrates the skin while simultaneously avoiding skin irritation. The skin includes an outer layer, the epidermis, whose bodily function is to provide a barrier to entry. The epidermis, although allowing water to pass through, generally resists chemical attack. Consequently, TTSs must be formulated carefully, to ensure adequate mass transport of the active ingredient through the epidermis. The use of penetration enhancers, which promote penetration of the active ingredient through the various skin layers, are widely known. Penetration enhancers are especially well known in conjunction with non-water-based TTSs, as evidenced in cited US 733 incorporating Copherol® to aid pramipexol in penetrating the skin.

Applicants have further determined that the construction of the TTS layers can induce a significant lag time in delivering the active ingredient to the skin's surface. Applicants have more particularly determined that conventional single-layered TTSs, such as the TTS of US 733, formed from pressure sensitive adhesive matrices exhibit a significant lag time before delivering an adequate pramipexol flux. A single layered TTS incorporating 10 % by weight pramipexol takes approximately 32 hours to develop a flux rate greater than 5 $\mu g/cm^2$ hr, for example, as illustrated in Figure 1 of the Application-as-filed.

Quite unexpectedly, Applicants have determined that TTSs incorporating two active-ingredient containing layers formed from pressure sensitive adhesive addresses this lag time, providing an adequate pramipexol flux within 24 hours of application. For example, a two layered TTS incorporating only 3 % by weight pramipexol in the skin side layer and 40 % by weight pramipexol in the outermost layer takes less than 24 hours to develop a flux rate greater than 5 $\mu g/cm^2$ hr, as illustrated in Figure 2 of the Application-as-filed. The elevated flux rates provided by the claimed invention translates into a much quicker and more prolonged efficacy for the patient.

Surprisingly, Applicants have further found that the inventive TTSs, incorporating a quite elevated pramipexol loading within its outermost polymer layer, does not require an adhesive intermediary layer, as taught by conventional wisdom and evidenced in newly cited US 028. Applicants have thus additionally determined that the inventive TTSs incorporating highly loaded carboxyl-group-free polyacrylate pressure-sensitive-adhesive retains sufficient adhesion to skin to also avoid the use of a covering plaster. This finding was altogether unexpected, as conventional wisdom instead clearly taught the need for an adhesive intermediary layer, as evidenced by US 028, and/or covering plaster, as evidenced in US 842. The absence of such intermediary layer and/or covering plaster translates into a thinner, more comfortable TTS for the wearer.

Accordingly, the claims are directed to advantageous transdermal therapeutic systems for continuous administration of pramipexol that include both first and second pramipexol-containing polymer layers formed from pressure-sensitive adhesive polymer based on carboxyl group-free polyacrylates, in which the first pramipexol-containing polymer layer, disposed directly on the backing layer, includes pramipexol in an elevated proportion of between 25 up to 75 % by weight and the second pramipexol-containing layer, disposed toward the skin, includes pramipexol in a more modest proportion of 2 to 10% by weight, with the resulting TTS providing a flux rate of greater than 5 $\mu g/cm^2$ after only 24 hours after application, with such beneficial flux rate continuing for up to 72 hours after administration, as recited in Claim 1 as-amended.

In especially beneficial embodiments, the first and second active ingredient-containing polymer layers are formed from pressure-sensitive adhesive polymer consisting of carboxyl group-free polyacrylates that do not comprise water or an aqueous dispersion, and the transdermal therapeutic system releases the active ingredient pramipexol with a flux rate greater than 5 $\mu g/cm^2$ hr over the period between 24 hours after administration to 72 hours after administration in the absence of a penetration-promoter or covering plaster, as recited in newly added Claim 19.

In particularly expedient embodiments, the first and second active ingredient-containing polymer layers consist solely of pramipexol and carboxyl group-free polyacrylate pressure-sensitive adhesive, as recited in newly added Claim 20.

In advantageous embodiments, the inventive TTSs provide the foregoing beneficial flux rates without resort to an additional top pressure sensitive adhesive plaster for fixing to the skin, as recited in Claim 18 as-amended.

The cited references do not teach or suggest the claimed invention.

Applicants particularly respectfully submit that the cited references, either alone or in combination does not teach or suggest the inventive TTSs containing a first active ingredient layer formed from carboxyl-group-free polyacrylate pressure-sensitive adhesive polymer that contains up to 75 % pramipexol disposed directly on a backing layer, much less such a TTS providing a flux rate greater than 5 $\mu g/cm^2$ hr up to 72 hours after administration.

And the combination most certainly does not teach or suggest such TTSs that do not include penetration enhancer or a covering plaster, as reflected in Claims 18 through 20.

The primary reference, US 733, expressly teaches a moderate amount of pramipexole within a single layered matrix that further includes a penetration enhancer. The newly cited references are not directed to pramipexol. US 094 merely incorporates apomorphine in amounts of up to 10 % into a silicone adhesive that further contains a penetration-enhancer. US 028 incorporates any of a laundry list of active ingredients into silicon rubber or the like in undisclosed amounts. US 028 does, however, expressly teach that elevated quantities of active ingredients within an adhesive layer require an additional adhesive intermediary layer between the adhesive layer and the backing layer. US 842 merely teaches single layered pramipexole TTSs formed from water-based polyacrylate that further include a covering plaster. WO 136 merely disloses ropinirole in undisclosed amounts within a water-based matrix sufficient for once-a-day application.

Accordingly,the cited references, considered either alone or in combination, simply do not teach or suggest the inventive multi-layered TTSs containing an active ingredient layer formed from carboxyl-group-free polyacrylate pressure-sensitive adhesive polymer that contains up to 75 % pramipexol disposed directly on a backing layer, much less such a TTS providing a flux rate greater than 5 $\mu g/cm^2$ hr up to 72 hours after administration.

And the combination most certainly does not teach or suggest such TTS that do not include penetration enhancer or a covering plaster, as reflected in Claims 18 through 20.

Applicants respectfully reiterate that US 733 is generally directed to single layer TTSs providing improved shelf stability that include a maximum of 15 % by weight active ingredient. (Col. 2, line 66 - Col. 3, line 2 and Col. 2, lines 19 - 20). US 733 provides a generic laundry list of suitable pressure sensitive adhesives, including polyurethane. (Col. 3, lines 23 – 26). In contrast to the recited carboxyl group-free polyacrylates, US 733 instead expressly teaches acrylic acid and methacrylic acid as suitable monomers within its matrix polymer. (Col. 3, lines 50 – 52). US 733 merely generically notes that its systems may include one or more matrix layers. (Col. 2, lines 40 – 45). US 733 notes that permeation enhancers may be included "where applicable." (Col. 2, lines 40 – 45). The working examples of US 733 expressly teach the incorporation of permeation enhancer, i.e. Copherol®, in conjunction with acrylic-based matrix layers; however. (Col. 4, line 43 – Col. 6, line 27 (Exs. 1 - 3)). The working examples of US 733 further teach the incorporation of 2.5 to 3 weight % active ingredient within a single layer of acrylic-based matrix. (Col. 4, line 43 – Col. 6, line 27 (Exs. 1 - 3)).

US 733 thus does not teach or suggest the claimed invention.

As has been indicated by the Examiner, US 733 does not teach transdermal therapeutic systems in which the active ingredient pramipexol has a flux rate greater than 5 $\mu g/cm^2$ hr over the period between 24 hours after administration to 72 hours after administration.

US 733, generically noting any of a laundry list of adhesives and a maximum of 15% active ingredient, further does not teach or suggest that a first active ingredient-containing polymer layer formed from carboxyl group-free polyacrylates could be formulated to include from 25 up to 75 % by weight pramipexol, as additionally recited in Claim 1.

And US 733 most certainly does not teach or suggest that such a highly loaded pramipexol-containing polymer layer could be directly disposed upon a backing layer, as recited in Claim 1 as-amended. Applicants respectfully submit that conventional wisdom would instead indicate that an adhesive intermediary layer would be required, as taught in newly cited US 028.

US 733, clearly teaching penetration enhancer with polyacrylate matrices, likewise fails to teach or suggest advantageous transdermal therapeutic systems in which the pressure-sensitive adhesive polymer consists of carboxyl group-free polyacrylates and that further provide the recited pramipexol flux rate in the absence of a penetration-promoter, as recited in Claim 18 and newly added Claim 19.

Nor does US 733 teach or suggest advantageous embodiments in which the first and second active ingredient-containing polymer layers consists of pramipexol and carboxyl group-free polyacrylate pressure-sensitive adhesive, as recited in newly added Claim 20. As noted above, US 733 instead clearly teaches the incorporation of a penetration-promoter.

Accordingly, Applicants respectfully submit that the claimed invention is patentable in light of US 733, considered either alone or in any combination with the remaining art of record.

The secondary references do not overcome the deficiencies in US 733.

US 094 is directed to apomorphine, an active ingredient having an altogether different chemical constitution from the recited pramipexol. (Col. 2, lines 41 – 44). The apomorphine of US 094 may be administered as a water soluble gel composition or as a transdermal patch. (Col. 2, lines 44 – 50). The water soluble gel includes up to 40 % water, ensuring effective topical delivery and bioavailability. (Col. 2, lines 56 – 60). In the alternative, the apomorphine of US 094 may be delivered from discoid dosage form from a silicone-adhesive matrix containing a permeation enhancer. (Col. 3, lines 39 – 42; Col. 8, lines 1 – 16; Col. 9, lines 31 – 41 and Col. 12, lines 41 - 44). The apomorphine may be present within the discoid matrix layer in amounts of up to 10 % by weight. (Col. 8, lines 42 – 44). By comparison, the permeation enhancer, which includes butylated hydroxytoluene and the like, may be present in amounts of up to about 30 % by weight. (Col. 3, lines 44 – 51).

Evidencing conventional wisdom, the permeation enhancer is said to "increase[s] the permeability of the treated area of skin to apomophine to a magnitude such that sufficient apomorphine is absorbed to provide a therapeutically effective level of apomorphine in the bloodstream." (Col. 5, lines 8 – 12). US 094 goes on to teach that "the permeation enhancer modulates the rate at which the skin absorbs the apomorphine." (Col. 5, lines 15 – 20). US 094 generically indicates that its multi-layered discoid patches contain both apomorphine and penetration enhancer, which may "differ in amount in each layer." (Col. 8, lines 63 – 65). The working examples indicate that the transdermal patches of US 094 deliver 100 % of the apomorphine within 3 hours or less. (Col. 21, lines 52 - 58).

US 094 thus does not teach or suggest the claimed invention.

US 094, teaching apomorphine delivered within 3 hours or less, does not teach or suggest transdermal therapeutic systems in which the active ingredient is pramipexol, much less such systems in which the pramipexol has a flux rate greater than 5 $\mu g/cm^2$ hr for up to 72 hours after administration.

US 094, expressly teaching a maximum of 10 % apomorphine, further does not teach or suggest that a first active ingredient-containing polymer layer formed from carboxyl group-free polyacrylates could be formulated to include from 25 up to 75 % by weight pramipexol, as additionally recited in Claim 1.

Thus US 094 can not teach or suggest that such a highly loaded pramipexol-containing polymer layer could be directly disposed upon a backing layer, as recited in Claim 1 as-amended.

US 094, requiring a permeation enhancer for sufficient apomorphine delivery, likewise fails to teach or suggest advantageous transdermal therapeutic systems in which the pressure-sensitive adhesive polymer consists of carboxyl group-free polyacrylates and that further provide the recited pramipexol flux rate in the absence of a penetration-promoter, as recited in Claim 18 and newly added Claim 19.

Nor does US 094 teach or suggest advantageous embodiments in which the first and second active ingredient-containing polymer layers consists of pramipexol and carboxyl group-free polyacrylate pressure-sensitive adhesive, as recited in newly added Claim 20. As noted above, US 094 instead clearly teaches the incorporation of a permeation-enhancer.

Accordingly, Applicants respectfully submit that the claimed invention is patentable in light of US 094, considered either alone or in any combination with the remaining art of record

Newly cited US 028 likewise fails to cure the deficiencies in the foregoing references.

US 028 generically discloses medical bandages containing therapeutically active agents in up to 12 layers. (Col. 2, lines 4 – 21 and Col. 6, lines 13 - 17). Suitable therapeutically active agents include any of a laundry list of medicaments, including antibiotics, hormones, anti-migraine agents and the like. (Col. 4, lines 16 – 26). US 028 does not teach a suitable range of amounts of active agent within its reservoir layers, but does expressly note that elevated quantities of active ingredients may cause the layer to lose its adhesive power, and thus require an additional adhesive intermediary layer.(Col. 6, lines 28 – 31 and Col. 4, lines 27 - 33). The therapeutically active agent is contained in a "polymer matrix," which US 028 goes on to define as a "base polymer and usual additives." (Col. 3, lines 47 – 52). Suitable polymer bases include caoutchouc, a natural rubber, and polyurethane. (Col. 3, lines 54 – 58). The working examples are directed to nitroglycerine bandages worn for up to 26 hours. (Col. 9, lines 5 – 23). The working examples of US 028 contain an adhesive intermediary layer. (Col. 8, lines 25 – 28 and Col. 10, lines 47 – 48).

US 028 thus does not teach or suggest the claimed invention.

US 028, teaching the delivery of nitroglycerine within 26 hours, does not teach transdermal therapeutic systems in which the active ingredient is pramipexol, much less such

systems in which the pramipexol has a flux rate greater than 5 $\mu g/cm^2$ hr for up to 72 hours after administration.

US 028, silent as to active ingredient loadings into its laundry list of matrices, further does not teach or suggest that a first active ingredient-containing polymer layer formed from carboxyl group-free polyacrylates could be formulated to include up to 75 % by weight pramipexol, as additionally recited in Claim 1.

And US 028 most certainly does not teach or suggest that such a highly loaded pramipexol-containing polymer layer could be directly disposed upon a backing layer, as recited in Claim 1 as-amended. US 028 instead clearly teaches away from such advantageous embodiments by cautioning that elevated quantities of active ingredients may cause the layer to lose its adhesive power, and thus require an additional adhesive intermediary layer. In fact, the working examples of US 028 include such an adhesive intermediary layer.

US 028, expressly teaching that its polymer matrix includes a base polymer and the "usual additives," likewise fails to teach or suggest advantageous transdermal therapeutic systems in which the pressure-sensitive adhesive polymer consists of carboxyl group-free polyacrylates and that further provide the recited pramipexol flux rate in the absence of a penetration-promoter, as recited in Claim 18 and newly added Claim 19.

US 028 likewise fails to teach or suggest advantageous embodiments in which the first and second active ingredient-containing polymer layers consists of pramipexol and carboxyl group-free polyacrylate pressure-sensitive adhesive, as recited in newly added Claim 20. As noted above, US 028 instead clearly teaches the incorporation of the "usual additives" in its polymer matrix.

Accordingly, Applicants respectfully submit that the claimed invention is patentable in light of US 028, considered either alone or in any combination with the remaining art of record

Previously cited US 842 likewise fails to teach or suggest the claimed invention.

US 842 is directed to single-active-ingredient-layer TTSs that further include a covering plaster which "secure[s] the system to the skin." (US 842, Col. 2, lines 11 – 15). US 842 broadly notes that its active ingredient layer may be formed from "emulsion polymerized polyacrylate," i.e. a water-based polyacrylate, preferably Eudragit® NE 30 D (US 842, Col. 1, line 64 – Col. 2, line 2 and Col. 2, lines 18 – 20). As noted in the Application as-filed on Page 3, line 35 through Page 4, line 1, Eudragit® NE 30 D is not a pressure sensitive adhesive. Consequently, the backing layer is formed as a "covering plaster" so that it may secure the system to the skin. (US 842, Col. 2, lines 11 – 15). The working examples of US 842 include 9 wt % active substance within a single layer. (US 842, Col. 2, lines 53 – 62). US 842 curiously provides concentration data beginning on the 3rd day and ending on the 4th day following application. (US 842, Col. 3, lines 2 – 12). In vitro investigations on samples of the TTSs indicate that about 70 % of the amount of active ingredient had been delivered after only 4 days and that only about a further 10% of the amount of active ingredient originally present in the reservoir can be released in the subsequent three days. (US 842, Figure 1, as interpreted in the Application-as-filed on Page 4, lines 9 – 14). The primary reference, US 733, further teaches that pramipexole decomposes "very rapidly" within the polyacrylate of US 842 and that the active ingredient would additionally crystallize out. (US 773, Col. 1, lines 57 – 65).

US 842 thus does not teach or suggest the claimed invention.

US 842, solely directed to single-active-ingredient-layer TTSs, does not teach transdermal therapeutic systems in which the active ingredient pramipexol has a flux rate greater than 5 $\mu g/cm^2$ hr at 24 hours after administration, as recited in the claimed invention. Applicants respectfully reiterate that single-layered-active-ingredient TTSs would instead be expected to perform poorly at the 24 hour mark, as indicated in Figure 1 of the Application-as-filed.

US 842, teaching only a non-adhesive matrix layer, further does not teach or suggest that a first active ingredient-containing polymer layer formed from carboxyl group-free polyacrylate

pressure-sensitive adhesive could be formulated to include up to 75 % by weight pramipexol, as additionally recited in Claim 1.

US 842 thus most certainly does not teach or suggest that such a highly loaded pramipexol-containing pressure sensitive adhesive polymer layer could be directly disposed upon a backing layer, as recited in Claim 1 as-amended.

US 842, requiring a top plaster to adhere its non-adhesive matrix, likewise fails to teach or suggest advantageous transdermal therapeutic systems providing the recited pramipexol flux rate that require no additional top plaster for fixing to the skin, as recited in Claim 18 and newly added Claim 19.

And US 842 most certainly does not teach or suggest advantageous embodiments in which the first and second active ingredient-containing polymer layers consists of pramipexol and carboxyl group-free polyacrylate pressure-sensitive adhesive, as recited in newly added Claim 20. As noted above, US 028 instead clearly requires a non-adhesive matrix.

Accordingly, Applicants respectfully submit that the claimed invention is patentable in light of US 842, considered either alone or in any combination with the remaining art of record.

WO 136 is merely directed to the use of ropinirole in free base form as an active ingredient in either membrane-based or maxtrix-based transdermal devices. (Page 1, line 34 – Page 2, line 5 and Page 2, lines 15 - 21). WO 136 is curiously silent as to the amount of ropinirole free base within its formulations, other than to note that sufficient ropinirole is to be provided for a 24 hour period, as it is intended for once-a-day application. (Page 3, lines 24 – 26). The working examples of WO 136 include a single drug-containing layer formed from either a saline/propylene glycol "vehicle" within the membrane-based TTS or a hydrogel within the matrix-based TTS. (Page 4, lines 14 – 36). The hydrogel of WO 136 is formed from polyvinyl alcohol ("PVA") and polyvinylpyrrolidone ("PVP"). (Page 4, lines 33 – 34). The hydrogel further includes glycerin as an excipient. (Page 4, line 34). The working examples

include either a silicone adhesive or undisclosed adhesive. (Page 4, lines 14 – 36). WO 136 further teaches that a penetration enhancer may be added. (Col. 2, lines 24 – 25).

WO 136 merely provides extended penetration data based upon the percutaneous penetration of the saturated saline or saline/propylene glycol vehicle alone. (Page 5, lines 1 – 21). Applicants respectfully reiterate that WO 136 does not teach or suggest that its TTSs provide such extended release, but instead tests suspensions of ropinirole to determine its "relative potential" in transdermal systems. (Page 5, lines 3 – 5). WO 136 goes on to note that, based on its initial solution study, a sufficient quantity of ropinirole free based was found to penetrate the skin for a 24 hour period and a patch delivering a sufficient quantity of ropinirole could "potentially" be formed. (Page 6, lines 7 – 9). Applicants respectfully submit that working patches incorporating the tested vehicle would further include a membrane, as taught in Example 1 of WO 136.

WO 136 thus does not teach or suggest the claimed invention.

WO 136, teaching the delivery of ropinirole within 24 hours, does not teach transdermal therapeutic systems in which the active ingredient is pramipexol, much less such systems in which the pramipexol has a flux rate greater than 5 $\mu g/cm^2$ hr for up to 72 hours after administration.

WO 136, silent as to the ropinirole loadings within its PVA/PVP hydrogel, further does not teach or suggest that a first active ingredient-containing polymer layer formed from carboxyl group-free polyacrylate pressure sensitive adhesive could be formulated to include up to 75 % by weight pramipexol, as additionally recited in Claim 1.

And WO 136 most certainly does not teach or suggest that such a highly loaded pramipexol-containing polymer layer formed from carboxyl group-free polyacrylate pressure sensitive adhesive could be directly disposed upon a backing layer, as recited in Claim 1 as-amended. WO 136 instead merely teaches a PVA/PVP hydrogel in contact with a backing foil.

WO 136 likewise fails to teach or suggest advantageous transdermal therapeutic systems in which the pressure-sensitive adhesive polymer consists of carboxyl group-free polyacrylates and that further provide the recited pramipexol flux rate in the absence of a penetration-promoter, as recited in Claim 18 and newly added Claim 19. WO 136 instead teaches a PVA/PVP hydrogel or saline/propylene glycol vehicle and further teaches the use of penetration enhancers.

And WO 136 most certainly does not teach or suggest advantageous embodiments in which the first and second active ingredient-containing polymer layers consists of pramipexol and carboxyl group-free polyacrylate pressure-sensitive adhesive, as recited in newly added Claim 20. WO 136 instead clearly requires ropinirole within a PVA/PVP hydrogel or a saline/propylene glycol vehicle. Applicants further respectfully reiterate that the diffusional properties of ropinorole within either the tested saline/propylene glycol solution or the prospective polyvinyl alcohol/ polyvinylpyrrolidone hyrogel can not be imputed to the inventive transdermal systems incorporating pramipexole within carboxyl group-free polyacrylate pressure-sensitive adhesive layers.

Accordingly, Applicants respectfully submit that the claimed invention is patentable in light of WO 136, considered either alone or in any combination with the remaining art of record

Applicants respectfully submit that here would have been no motivation to have combined US 733, US 094, US 028, US 842 and WO 136. Applicants particularly respectfully make of record that one skilled in the art would not transfer the teachings from other active ingredients, e.g. apomorphine (US 094), anti-migraine agents (US 028), ropinirol (WO 136) to pramipexol, as these active ingredients have a significantly different chemical constitution and associated physical properties.

However, even if Applicants had combined US 733, US 094, US 028, US 842 and WO 136 (which they did not), the claimed invention would not have resulted.

As noted above, the cited references, considered either alone or in combination, simply do not teach or suggest the inventive TTSs containing a first active ingredient layer formed from carboxyl-group-free polyacrylate pressure-sensitive adhesive polymer that contains up to 75 % pramipexol disposed directly on a backing layer, much less such a TTS providing a flux rate greater than 5 $\mu g/cm^2$ hr up to 72 hours after administration. Instead, the only teaching as to highly loaded adhesive matrices is that extreme active ingredient loadings are highly detrimental to the structural integrity of TTSs and thus requires an intermediate adhesive layer.

US 733 at best suggests multiple active ingredient layers including from 2 to 15 % active ingredient. Newly cited US 094, teaching a maximum of 10 % apomorphine within its layers, does not cure this deficiency. Newly cited US 028, silent as to recommended active ingredient loadings, expressly teaches that elevated amounts of active ingredients would require an intermediate adhesive layer adjacent the backing layer to provide structural integrity. US 842 does not teach or suggest loading a pressure sensitive adhesive, and requires a covering layer to impart adhesion to the skin. WO 136 merely teaches ropinirole in an undisclosed amount within a PVA/PVP hydrogel.

Consequently, the combination at best suggests TTS incorporating multiple active ingredient layers including from 2 to 15 % active ingredient that further include an intermediate adhesive layer to provide structural integrity and a covering layer to impart adhesion to the skin.

And the combination most certainly does not teach or suggest transdermal therapeutic systems incorporating first and second active ingredient-containing polymer layers formed from pressure-sensitive adhesive polymer consisting of carboxyl group-free polyacrylates that do not include water or an aqueous dispersion that further provide such advantageous pramipexol flux rates in the absence of excipients or penetration-promoters and further without a top plaster, as recited in Claims 18 through 20. US 733 expressly teaches the incorporation of a penetration promoter in conjunction with polyacrylate pressure sensitive adhesives. US 094 likewise indicates that its discoid patches contain penetration enhancer. US 028 teaches use of the "usual

additives" in dispensing antibiotics and the like from natural rubber. WO 136 expressly teaches active ingredient within a hydrogel or saline solution. US 842 is directed to TTSs incorporating an aqueous based non-adhesive matrix requiring a top plaster.

Nor does the combination teach or suggest such TTS in which the first and second active ingredient-containing polymer layers consist of pramipexol and carboxyl group-free polyacrylate pressure-sensitive adhesive, as recited in Claim 20. US 733 instead clearly teaches the incorporation of a penetration enhancer. The remaining references do not cure this deficiency.

Accordingly, Applicants respectfully submit that the claimed invention is patentable in light of each of US 733, US 094, US 028, US 842 and WO 136, considered either alone or in any combination with the remaining art of record.

Claim 16 is likewise patentable in further view of US 944.

US 944 is directed to formulations for the topical or transdermal delivery of 1-isobutyl-1H-imidazo[4,5-c]-quinolin-4-amine, an anti-viral, using isostearic and/or oleic fatty acid. (Col. 1, lines 49 – 63 and Col. 2, lines 1 - 4). The fatty acid may be included in amounts of up to 45 % by weight. (Col. 3, lines 49 – 52). The 1-isobutyl-1H-imidazo[4,5-c]-quinolin-4-amine may be present in amounts of up to 9 % by weight. (Col. 3, lines 43 – 46). US 944 indicates that suitable adhesives include 4 to 9 % acrylic acid or methacrylic acid reinforcing monomer. (Col. 6, lines 23 – 24 and lines 33 - 34). US 944 is merely directed to single-layered transdermal devices. (Col. 16, lines 45 – 65). US 944 further indicates that skin penetration enhancers may be incorporated, in amounts of up to 25 %. (Col. 2, lines 48 – 51 and Col. 7, lines 23 - 38).

Applicants respectfully submit that US 944 does not teach or suggest the claimed invention.

US 944, solely directed to 1-isobutyl-1H-imidazo[4,5-c]-quinolin-4-amine formulations, does not teach or suggest the inventive transdermal therapeutic systems incorporating pramipexol.

Nor does US 944, directed to conventional single layer TTSs including up to 9 % active ingredient, teach or suggest such transdermal therapeutic systems including first and second active ingredient-containing polymer layers, much less such layers in which the first active ingredient-containing layer incorporates up to 75 % by weight pramipexol and the second active ingredient-containing layer incorporates up to 10 % by weight pramipexol.

And US 944, expressly teaching 4 to 9 % acrylic acid or methacrylic acid reinforcing monomer, most certainly does not teach or suggest the inventive transdermal therapeutic systems in which the active ingredient-containing layers are formed from carboxyl group-free polyacrylates, as further recited in Claim 16.

US 944 likewise fails to teach or suggest such transdermal therapeutic system that release the active ingredient pramipexol with a flux rate greater than 5 $\mu g/cm^2$ hr over the period between 24 hours after administration to 72 hours after administration.

Accordingly, Applicants respectfully submit that US 944 does not teach or suggest Claim 16, considered either alone or in any combination with the remaining art of record.

Applicants respectfully submit that there likewise would have been no motivation to have combined US 733, US 094, US 842, WO 136 and US 944. However, even if Applicants had combined the foregoing references (which they did not), the claimed invention would not have resulted.

The combination particularly does not teach or suggest that advantageous transdermal therapeutic systems including an outermost active ingredient-containing polymer layer comprising up to 75 % by weight pramipexol disposed directly on a backing layer and a second active ingredient-containing polymer layer comprising between 2 and 10 % by weight pramipexol, in which the outermost and second active ingredient-containing polymer layers are formed from pressure-sensitive adhesive polymer consisting of carboxyl group-free polyacrylates would result in transdermal therapeutic systems releasing pramipexol at a flux rate greater than 5 $\mu g/cm^2$ h from 24 to 72 hours after administration.

US 733 teaches a maximum of 15 % active ingredient within a single layer. Newly cited US 094, teaching a maximum of 10 % apomorphine within its layers, does not cure this deficiency. Newly cited US 028, silent as to recommended active ingredient loadings, expressly teaches that elevated amounts of active ingredients would require an intermediate adhesive layer adjacent the backing layer to provide structural integrity. US 842 does not teach or suggest loading a pressure sensitive adhesive, and requires a covering layer to impart adhesion to the skin. WO 136 merely teaches ropinirole in an undisclosed amount within a PVA/PVP hydrogel. US 994 merely teaches the incorporation of up to 9 % of a particular antiviral within carboxyl-group containing adhesive.

Accordingly, Applicants respectfully submit that Claim 16 is likewise patentable in light of each of US 733, US 094, US 842, WO 136, and US 994 considered either alone or in any combination.

CONCLUSION

It is respectfully submitted that Applicants have made a significant and important contribution to the art, which is neither disclosed nor suggested in the art. It is believed that all of pending Claims 1 through 3, 6 through 12 and 14 through 20 are now in condition for immediate allowance. It is requested that the Examiner telephone the undersigned if any questions remain to expedite examination of this application.

It is not believed that extensions of time or fees are required, beyond those which may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time and/or fees are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required is hereby authorized to be charged to Deposit Account No. 50-2193.

Respectfully submitted,

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CERTIFICATE OF ELECTRONIC TRANSMISSION

I hereby certify that this correspondence is being transmitted to the United States Patent and Trademark Office PAIR Webpage via the electronic filing system in accordance with 37 CFR § 1.6(a)(4) on March 2, 2010.

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